Effective Attraction Interactions between Like-charge Macroions Bound to Binary Fluid Lipid Membranes

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Abstract

Using integral equation theory of liquids to a binary mixed fluid lipid membrane, we study the membrane-mediated interactions between the macroions and the redistribution of neutral and charged lipids due to binding macroions. We find that when the concentration of binding macroions is infinitely dilute, the main contribution to the attractive potential between macroions is the line tension between neutral and charged lipids of the membrane, and the bridging effect also contributes to the attraction. As the relative concentration of charged lipids is increased, we observe a repulsive - attractive - repulsive potential transition due to the competition between the line tension of lipids and screened electrostatic macroion-macroion interactions. For the finite concentration of macroions, the main feature of the attraction is similar to the infinite dilution case. However, due to the interplay of formation of charged lipid - macroion complexes, the line tension of redistributed binary lipids induced by single macroion is lowered in this case, and the maximum of attractive potential will shift toward the higher values of the charged lipid concentration.

Keywords: Two-dimensional fluid membrane, membrane-mediated interaction, integral equation theory, line tension, bridging effect.

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I. INTRODUCTION

Generally, it is believed that, in the physiological condition, biomembranes are quasi two-dimensional (2D) fluid mixtures, composed of a wide variety of protein and lipid molecular species. The protein-protein, protein-lipid, and lipid-lipid interactions in and on the membranes are very important to the functions of the cell, such as ligand-receptor interactions (1), membrane rafts (2), and the formation of lipids domains and membrane budding (3), etc. Most of these problems are complex and not well understood yet. Recently, there is an increasing interest in understanding the electrostatic binding of charged macroions to the oppositely charged lipid membrane both experimentally and theoretically (4-13). Because of lipid's fluidity in the membrane, when the charged macroions are bound to the membrane, the oppositely charged lipids would migrate to the binding sites. This process would compete with the mixing entropic effects of different lipid species, and at equilibrium, the minimum of free energy is required. There are several theoretical works characterizing such a process (9-13). One of the models takes into account the entropy contributions of lipids and membrane-associated proteins to the free energy in the incompressible limit. Combined with the nonlinear Poisson-Boltzmann (PB) equation, May and Ben-Shaul have obtained the local lipid composition and the adsorption free energy in the single protein case, and accessed the influence on these physical quantities when the concentration of binding proteins is finite (9). By introducing a parameter χ characterizing the extent of non-ideal lipid mixing in the mean field approximation, they were able to give the phase behavior of charged lipid membranes with the binding peripheral proteins. The existence of a two-dimensional phase separation suggests that there is an effective lateral attractive potential between the binding proteins. However, the nonlinear PB theory itself does not introduce such a potential (14), and thus the authors argued that the attraction must be mediated by the membranes (10,12). To numerically solve the nonlinear PB equation simply and efficiently, most of the theoretical work mentioned above adopted cylindrical symmetry with the axis through the center of the macroion and normal to the charged membrane. Such a symmetric consideration make it difficult to calculate the effective pair potential between the macroions. In fact, there have been no systematic theoretical studies into detailed calculation of effective interactions between binding macroions. The specific form of membrane-mediated like-charge attractive potential has not been clarified, and the mechanism is still unclear.

In the present paper, we establish a simple model of the fluid membrane and the binding macroions, to examine the lipid-mediated effective pair potential between binding macroions. Actually, the calculation of the effective pair potential is very important to understanding the phase behavior of soft matters. Recently, the effective potential in ionic solution that is beyond the description of the Derjaguin-Landau-Verwey-Overbeek (DLVO) theory receives great recognition (15), and it is believed that it will have further applications in biological systems (16,17). The most counterintuitive phenomenon is the effective attraction between like-charge objects. Most of these phenomena can be understood as the strong correlation effects of multivalent counter-ions (18-21). However, the long-range attraction between like-charge spheres confined in parallel glass walls is still an open question both for experimental and theoretical studies (22-24). It is believed that such a long-range attraction is mediated by the substrate parallel glass walls because of confinement, but the mechanism is still not revealed theoretically (16). On the contrary, the theoretical understanding of effective potential between the macroions mediated by the fluid membrane will be much more complicated, but is relatively unexplored. There are several approaches to get the effective potential theo-

retically. Here we will adopt the integral equation theory which is an accurate and powerful tool to explore the microscopic short-range structure of liquids (25,26), and recently, it has been applied successfully to explain the haloing effects of colloidal stabilization (27,28).

II. MODEL AND THEORY

It is well-known that biomembranes are a kind of lyotropic liquid crystals, and the lipid is an amphiphilic molecule composed of a hydrophilic head and one or two hydrophobic tail chains. In our model, we take the membrane as two-dimensional fluids composed of neutral and charged lipid species. The interactions between the lipids can be separated into two parts which are head-head and tail-tail interactions. The head-head interactions are treated as 2D hard core, while the tail-tail interactions are treated as 2D soft core to account for the repulsions between the tails originated from both enthalpy and entropy of chains. Thus the total pair potential $V_{\alpha\beta}(r)$ between α and β lipids with a lateral separation r can be written as:

$$V_{\alpha\beta}(r) = \begin{cases} \infty, & r \le r_{\alpha h} + r_{\beta h}, \\ \epsilon_{\alpha\beta} + v_{\alpha\beta}(r), & r_{\alpha h} + r_{\beta h} < r \le r_{\alpha s} + r_{\beta s}, \\ v_{\alpha\beta}(r), & r > r_{\alpha s} + r_{\beta s}, \end{cases} \tag{1}$$

where the indices α and β ($= c$ or n), indicate charged or neutral lipids. $r_{\alpha h}$ is α lipid's hard-core radius, and $r_{\alpha s}$ is α lipid's soft-core radius. $\epsilon_{\alpha\beta}$ is the soft repulsion between α and β lipids, therefore the interaction parameter characterizing the demixing extent of non-ideal mixed lipids is given by $\omega_{cn} = \epsilon_{cn} - (\epsilon_{cc} + \epsilon_{nn})/2$. For the sake of simplicity, we set $\epsilon_{cc} = \epsilon_{nn} = 0$, and thus $\omega_{cn} = \epsilon_{cn}$. However, we should point out that the real interaction between chains may be more complex as presented in literatures (29-31). $v_{\alpha\beta}(r)$ is the effective potential between the lipids introduced by charged heads in the absence of binding macroions, and it is obvious that $v_{nn}(r) = v_{cn}(r) = 0$.

The binding macroions can move, but confined in a two-dimensional plane which is parallel to the membrane but with a separation h, as reported in literature (13). For simplicity, the macroion is modelled as a hard sphere, which is uniformly charged on the surface. The pair potential $V_{pp}(r)$ between the macroions can be written as:

$$V_{pp}(r) = \begin{cases} \infty, & r \le 2r_p, \\ v_{pp}(r), & r > 2r_p, \end{cases} \tag{2}$$

where r_p is the hard-core radius of the macroion, $v_{pp}(r)$ is the screened electrostatic interaction in the absence of charged lipids. In the binding state, there is another pair potential to account for the interactions between the negatively charged lipids and positively charged macroions. Formally, it can be written as:

$$V_{pc}(r) = v_{pc}(r, h), \tag{3}$$

where r is the lateral separation between the lipids and macroions, and h is the minimal membrane-macroion distance (see Fig. 1). When h is fixed, the pair potential is only concerned with lateral distance r, so such a system can be effectively treated as a 2D fluid mixtures with pair potentials given above. Now, we can apply the two-dimensional integral equation theory to our model. The Ornstein-Zernike (OZ) equations for homogeneous

mixtures in two-dimensional case are given by

$$h_{\alpha\beta}(r) = c_{\alpha\beta}(r) + \sum_{\nu} \sigma_{\nu} \int c_{\alpha\nu}(|\mathbf{r} - \mathbf{r}'|) h_{\nu\beta}(\mathbf{r}') \mathrm{d}\mathbf{r}', \tag{4}$$

where $h_{\alpha\beta}(r)$ is defined by $h_{\alpha\beta}(r) \equiv g_{\alpha\beta}(r) - 1$. $g_{\alpha\beta}(r)$ is the radial distribution function, and $h_{\alpha\beta}(r)$ and $c_{\alpha\beta}(r)$ are the total and direct correlation function between two particles of species α and β, respectively. σ_{ν} is the number density of species ν. The summation is over all species, and the integral is performed over the two-dimensional space. Eq.(4) can be closed by the well-known Percus-Yevick (PY) or hypernetted-chain (HNC) approximations or other thermodynamic self-consistent approximations (25,26,32) which have different bridge functions $B_{\alpha\beta}(r)$. Formally, it can be written as follows:

$$g_{\alpha\beta}(r) = e^{-\beta V_{\alpha\beta}(r) + h_{\alpha\beta}(r) - c_{\alpha\beta}(r) + B_{\alpha\beta}(r)} \ . \tag{5}$$

In the HNC approximation, $B_{\alpha\beta}(r) = 0$, while in the PY approximation, $B_{\alpha\beta}(r) = \ln(1 + \gamma_{\alpha\beta}(r)) - \gamma_{\alpha\beta}(r)$ where $\gamma_{\alpha\beta}(r) \equiv h_{\alpha\beta}(r) - c_{\alpha\beta}(r)$.

III. DETAILS OF CALCULATION

The first step to do our calculation is to write down the specific form of pair potentials. Here, however, we must fall back on some approximations. The most important thing that we care is whether the charges are screened near the membrane in the physiological condition. One might argue that since the charges cannot penetrate into the membrane, the electro-static interactions between charged macroions or lipids near the membrane will not be screened. Such a statement does not take into account the specific properties of the membrane and the solution. We know that the hydrophobic part of the cell membrane has a dielectric constant $\varepsilon_m \sim 2.1$ and a thickness around $6 \sim 7$ nm, while the solution, in the physiological condition, has a dielectric constant $\varepsilon_s \sim 80$ and the screening length $\lambda \sim 1$ nm (33). When a charge Q occurs in the solution near the membrane (within $3 \sim 4$ nm), it will form an image charge in the membrane with $Q' = \dfrac{\varepsilon_s - \varepsilon_m}{\varepsilon_s + \varepsilon_m} Q \approx Q$. Now most of screening charges are near the membrane within 1 nm, and these charges would form images in the hydrophobic part of the membrane. Therefore the charges are surrounded by screening charges even on the membrane, and the electrostatic interactions must be more or less screened. This justifies the use of screened potentials. The screened potentials can be written as follows:

$$\begin{cases} \beta v_{pp}(r) = \dfrac{Z_p^2 L_B}{r} e^{-r/\lambda}, \\ \beta v_{pc}(r) = \dfrac{Z_p Z_c L_B}{\sqrt{r^2 + (r_p + h)^2}} e^{-\sqrt{r^2 + (r_p + h)^2}/\lambda}, \\ \beta v_{cc}(r) = \dfrac{Z_c^2 L_B}{r} e^{-r/\lambda}, \end{cases} \tag{6}$$

where the Bjerrum length $L_B = \dfrac{\beta e^2}{4\pi\varepsilon_0\varepsilon_s}$, λ is the screening length of the solution, and $\beta = 1/k_B T$. Z_c and Z_p are the effective charges of charged lipids and macroions, respectively.

Substituting Eq.(6) into Eqs.(1)-(3) gives the pair potentials we adopt here. Combined with the hard-core repulsion of macroions, we can study the effects of the screening length, charges, and macroion's size, etc.

The three-component OZ equations are calculated in the k-space. With some algebra, it can be written in a form more suitable for numerical calculations, which is formally given by

$$\tilde{h}_{\alpha\beta}(k) = f_{\alpha\beta}(\sigma, \tilde{c}(k)), \tag{7}$$

where $\tilde{c}(k)= (\tilde{c}_{cn}(k), \tilde{c}_{np}(k), \tilde{c}_{pc}(k), \tilde{c}_{cc}(k), \tilde{c}_{nn}(k), \tilde{c}_{pp}(k))$ and $\sigma= (\sigma_c, \sigma_n, \sigma_p)$. In the limiting $\sigma_p \to 0$, the OZ equations in the k-space reduce to a two-component OZ equations of lipids:

$$\tilde{h}_{cc}(k) = \frac{\tilde{c}_{cc}(k) + \sigma_n(\tilde{c}^2_{cn}(k) - \tilde{c}_{cc}(k)\tilde{c}_{nn}(k))}{\tilde{D}(k)}, \tag{8a}$$

$$\tilde{h}_{nn}(k) = \frac{\tilde{c}_{nn}(k) + \sigma_c(\tilde{c}^2_{cn}(k) - \tilde{c}_{cc}(k)\tilde{c}_{nn}(k))}{\tilde{D}(k)}, \tag{8b}$$

$$\tilde{h}_{cn}(k) = \frac{\tilde{c}_{cn}(k)}{\tilde{D}(k)}, \tag{8c}$$

and coupling equations with macroions:

$$\tilde{h}_{pc}(k) = \frac{\tilde{c}_{pc}(k)(1 - \sigma_n\tilde{c}_{nn}(k)) + \sigma_n\tilde{c}_{cn}\tilde{c}_{pn}(k)}{\tilde{D}(k)}, \tag{9a}$$

$$\tilde{h}_{pn}(k) = \frac{\tilde{c}_{pn}(k)(1 - \sigma_c\tilde{c}_{cc}(k)) + \sigma_c\tilde{c}_{cn}\tilde{c}_{pc}(k)}{\tilde{D}(k)}, \tag{9b}$$

where $\tilde{D}(k) = (1 - \sigma_c\tilde{c}_{cc}(k))(1 - \sigma_n\tilde{c}_{nn}(k)) - \sigma_c\sigma_n\tilde{c}^2_{cn}(k)$.

The two-dimensional Fourier transformation of the isotropic system can be defined by

$$f(r) = \frac{1}{2\pi}\int_0^\infty k\tilde{f}(k)J_0(kr)\mathrm{d}k, \tag{10a}$$

$$\tilde{f}(k) = 2\pi\int_0^\infty rf(r)J_0(kr)\mathrm{d}r, \tag{10b}$$

where $J_0(x)$ is the zeroth-order Bessel function of the first kind. In numerical calculations, Eq.(10) is truncated and discretized in r-space and k-space. The discrete Fourier transformation adopt here is a slow method, but satisfies the orthogonality conditions (34,35) which are important in our calculation.

The OZ equations (8) are closed by the well-known PY approximation, which is good for short-range potential and predicts with a reasonable accuracy both structural and thermodynamic properties of the investigated system (25). For the short-range repulsion between the lipids studied here, it is obvious that the PY approximation is more suitable. On the other hand, macroion's effect can effectively be treated as an external field, and thus Eq.(9) is solved by combining with HNC approximation (26), which is better for the long-range potential. Finally, the integral equations are solved by using the Picard iteration scheme, and the equality (5) can be rewritten as follows:

$$c^{new}_{\alpha\beta}(r) = p[e^{-\beta V_{\alpha\beta}(r)+\gamma_{\alpha\beta}(r)+B_{\alpha\beta}(r)} - 1 - \gamma_{\alpha\beta}(r)] + (1-p)c^{old}_{\alpha\beta}(r), \tag{11}$$

where p is an adjustable parameter to achieve the best performance of iterations.

IV. RESULTS AND DISCUSSION

In the infinite-diluted case, the coupling between macroions has been ignored, and thus the distribution function of macroions can effectively be defined by $g_{pp}(r) = e^{-\beta V_{pp}^{eff}(r)}$. Because of the coupling between the macroions and the lipids, the explicit distribution function is written as follows:

$$g_{pp}(r) = e^{-\beta V_{pp}(r) + \sigma_c \int h_{pc}(\mathbf{r}')c_{pc}(|\mathbf{r}\text{-}\mathbf{r}'|)\mathrm{d}\mathbf{r}' + \sigma_n \int h_{pn}(\mathbf{r}')c_{pn}(|\mathbf{r}\text{-}\mathbf{r}'|)\mathrm{d}\mathbf{r}'}, \tag{12}$$

namely the effective pair potential between macroions is

$$\beta V_{pp}^{eff}(r) = \beta V_{pp}(r) - \sigma_c \int h_{pc}(\mathbf{r}')c_{pc}(|\mathbf{r}\text{-}\mathbf{r}'|)\mathrm{d}\mathbf{r}' - \sigma_n \int h_{pn}(\mathbf{r}')c_{pn}(|\mathbf{r}\text{-}\mathbf{r}'|)\mathrm{d}\mathbf{r}'. \tag{13}$$

Here, the effects of the lipids on the macroions have been included in the effective pair potential between the macroions.

In the calculations presented below, we will restrict ourselves to the case that different species of lipids have the same size, $r_{ch} = r_{nh} = \tau$, $r_{cs} = r_{ns} = 4\tau/3$. The macroion's radius $r_p = 4\tau$ and the minimal membrane-macroion distance $h = 0.3\tau$. The Fourier transformation is truncated at $r \approx 90\tau$. The choice of the soft-core range seems a bit arbitrary, however, since such a range is fixed during our calculation, it will not obscure the results given below. To keep in line with the data appeared in Ref. (12), we choose $r_{ch} = r_{nh} = \tau = 4\mathring{A}$.

In Fig. 2 we show the effective potentials $\beta V_{pp}^{eff}(r)$ and the membrane-mediated potential $\beta V_{pp}^{m}(r) = \beta V_{pp}^{eff}(r) - \beta V_{pp}(r)$ for varying values of the demixing strength $\beta\omega_{cn}$ between neutral and charged lipids in the physiological condition ($\lambda = 10\mathring{A}, T = 300K$). The lipid concentration is fixed to be $\sigma_c\tau^2 = 0.055$ for charged lipids and $\sigma_n\tau^2 = 0.105$ for neutral lipids. We see that with increasing the repulsion between the neutral and the charged lipids, the attraction between macroions is greatly enhanced. The result supports the conclusion made by Hinderliter (7,8) from experiments and Monte-Carlo simulations. Obviously the effective potential is composed of two parts: one is from the contribution of the screened potential between macroions, and the other is mediated by the substrate membrane. The membrane-mediated attraction between macroions is within $4 \sim 5$ lipid's diameter from their surfaces.

Figure 3 shows the total correlation functions h_{pc} and h_{pn} with the lateral separation between macroion and lipid for different values of $\beta\omega_{cn}$. The correlations increases with the increase of $\beta\omega_{cn}$. Therefore, we can say that the attraction is mediated by the membrane through the correlations between the macroions and lipids. The resulting local density distribution $\sigma_\alpha(r)$ of the α lipids which deviates from the averaged bulk density σ_α, can be obtained by the relation $\sigma_\alpha(r) = (h_{p\alpha}(r) + 1)\sigma_\alpha$, when a macroion is in the center ($r = 0$). Interestingly, the density distribution of the lipids under the macroions is greatly modified by increasing the unmixing interaction $\beta\omega_{cn}$ between neutral and charged lipids, while the electrostatic interactions between the macroions and charged lipids keep unchanged. As $\beta\omega_{cn} = 0$, the solid line in Fig. 3 shows that the enrichment of charged lipids appears below the macroion, just through the screened Coulomb potential. Such a process can be balanced by the reduction of the mixing entropy and the increase of the repulsions between charged lipids. As $\beta\omega_{cn}$ turns on, it has a tendency to drive the same lipids to aggregate together. This will greatly increase the macroion-lipid correlations, as shown in Fig. 3, by enhancing the aggregation of the same lipids, due to a pre-enrichment of charged lipids below the macroion at $\beta\omega_{cn} = 0$.

The density profiles obtained here is similar to the results obtained from numerical solutions of the Poisson-Boltzmann equation (12,13). However in the present case, we have taken into account the correlation effects of species, and from the inset of Fig. 3(b), we find that after an enriched region of charged lipids, there is a depleted region of charged lipids where the number density of charged lipids is even smaller than the bulk case. Such a depleted effect of charged lipids will become stronger if the correlation effect is enhanced, as shown in Fig. 4 when Z_c is increased to 2e. This is in agreement with the statement about the multivalent system where the charge correlations become important, and thus there exists some counter-intuitive effects (16), which are beyond the descriptions of the PB theory.

For inhomogeneous mixing lipid system, if the interface between neutral and charged lipids is absolutely sharp on a molecular scale, the line tension will be directly proportional to the strength of unmixing $\beta\omega_{cn}$. Therefore, to some extent, Figs. 2 and 3 indicate that such an attractive effect can be enhanced by the line tension between different lipids. However, the weak attraction exists, even for the case $\beta\omega_{cn} = 0$ where the line tension contributes little to the attraction. It indicates a deeper screening of the interactions between binding macroions in the presence of charged lipids. The origin of such a potential is due to the bridging effect of charged lipids, namely two macroions jointly attract to the same set of charged lipids (28). Intuitively, it seems that there exists another effect, the so-called depletion attractive interaction (36), to contribute to $\beta V_{pp}^m(r)$. If we take the charged lipids-rich clusters under the binding macroions as static, it is possible to introduce such a depletion effect by hard-core repulsions between the clusters and the surrounding lipids. However, such a picture is naive. The charged lipids-rich regime is not static, but quite dynamic. The charged and neutral lipids can move in and out of the regime quiet freely, although the density profiles remain unchanged. Therefore, there is no static interactions between the charged lipids-rich regimes and the surrounding lipids. Such a dynamic effect is similar to that of Karanikas and Louis (28). To illustrate it clearly, we eliminate the bridging effect by introducing a pseudo potential between the binding macroions and the charged lipids:

$$\begin{cases} \beta V_{pc}(r) = \dfrac{Z_p Z_c L_B}{\sqrt{r^2 + (r_p + h)^2}} e^{-\sqrt{r^2+(r_p+h)^2}/\lambda}, & r \le 2r_p, \\ \beta V_{pc}(r) = 0, & r \ge 2r_p. \end{cases} \tag{14}$$

Such a potential does not allow two macroions to attract the same set of charged lipids, but the charged lipids-rich regime still exists. When we apply such a potential to our model in the case $\beta\omega_{cn} = 0$, the weak attraction disappears. This means that the bridging effect is dominant and there is no depletion effect under the present dynamic picture.

In Fig. 5, we change the relative composition of neutral and charged lipids, but the total number density of lipids is fixed. Interestingly, when σ_c is low, the effective potential is mainly repulsive, where the screened potential dominates over the interactions between macroions. With the increase of charged lipids, the membrane-mediated attraction becomes significant, and it competes with the screened potential at a distance about 2τ - 6τ and then forms an attractive well at that range. The attractive force saturates when $\sigma_c\tau^2 = 0.05$. Further increase of charged lipids will weaken the attractive potential, because the screened potential begins to dominate the system again.

To clarify the dominant contribution to the attractive potential, we can calculate the line tension by varying the number density of charged lipids, but $\beta\omega_{cn}$ is fixed. In the continuum limiting, the line tension is given by $\gamma_l = C(\omega_{cn}) \int d\mathbf{r} (\nabla\eta_c(r))^2$, where $\eta_c(r)$ is the local composition of charged lipids, and is estimated by $\eta_c(r) = \sigma_c(r)/(\sigma_c(r) + \sigma_n(r))$.

$C(\omega_{cn})$ is a coefficient relevant to ω_{cn}, here it is a constant, and thus we will present the result of $\gamma_l(r)$ in units of $C(\omega_{cn})$. In Fig. 6, the solid square line tension curve $\gamma_l(r)/C(\omega_{cn})$ is plotted as a function of the number density of charged lipids for the infinite-diluted case ($\sigma_p\tau^2 \to 0$). The line tension first increases with $\sigma_c\tau^2$, and then is decreased. The maximum line tension almost correspond to the deepest attractive potential of lipid-mediated interactions between macroions in Fig.5, and they are of the same order. We can conclude that the attractive potential increases with the line tension, depending upon two factors: the demixing interaction and the relative component between neutral and charged lipids. On the other hand, the effective attractive potential between macroions is always enhanced by increasing charged lipid's concentration $\sigma_c\tau^2$, namely the attraction due to the bridge effect monotonously increases with $\sigma_c\tau^2$. Therefore, there is a cooperation between the line tension and the bridging effect which jointly assists the attraction between macroions at the beginning stage of the increase of $\sigma_c\tau^2$, and for relatively large values of $\sigma_c\tau^2$, a competition occurs, since line tension will decrease with further increase of charged lipids. The fact that the line tension behavior in Fig.6 is in accordance with the effective potential well vs $\sigma_c\tau^2$ in Fig.5, clearly indicates that the line tension plays a vital important role in the membrane-mediated potentials, as argued in the Ref. (12) in the continuum limits of the membrane.

We now turn to discuss the effects of finite macroion concentration. In this case, the coupling between macroions cannot be ignored, and we have to solve the three-component OZ equations. The effective potential V_{pp}^{eff} between macroions can be obtained by an inverse process (37). After solving the integral equation Eq.(7), we can obtain the total correlation function $h_{pp}(r)$, and then the direct correlation function $\tilde{c}_{eff}(k)$ can be solved from the reduced one-component OZ equation:

$$\tilde{c}^{eff}(k) = \frac{\tilde{h}_{pp}(k)}{1 + \sigma_p \tilde{h}_{pp}(k)} \,. \tag{15}$$

The effective potential can be solved from the HNC approximation (24,37):

$$g_{pp}(r) = e^{-\beta V_{pp}^{eff}(r) + h_{pp}(r) - c^{eff}(r)}. \tag{16}$$

As $\sigma_p \to 0$, the present calculation reduces to the infinite-diluted case.

In Fig. 6, we firstly show the line tension as a function of $\sigma_c\tau^2$ for different macroion concentrations. We notice that on increasing binding macroions, the line tension is gradually decreased and the position of the maximum line tension shifts toward the higher values of σ_c. These two behaviors are of the same origin, because there exists a competing interplay of different macroions to recruit charged lipids. The competition will partially suppress the modification of lipid composition profiles induced by a single macroion, and thus the line tension decreases, in comparison with the case $\sigma_p\tau^2 \to 0$. Furthermore, we can expected that, at lower macroion concentrations, the charged lipid's profile saturates under a single macroion and the line tension reaches the maximum at a certain value of $\sigma_c\tau^2$. However, if the macroion concentration is increased, the charged lipid's concentration will not saturate at a former value of $\sigma_c\tau^2$. To achieve the maximum line tension, we should further increase the charged lipid's concentration, i.e., the maximum line tension occurs with a higher value of $\sigma_c\tau^2$ with the increase of binding macroions.

In Fig.7 we depict the effective potential for varying values of $\sigma_c\tau^2$ when $\sigma_p\tau^2 = 0.004$. We can see that the change of effective potentials has the same tendency as in the infinite-diluted

case. When the concentration of charged lipids is low, the screened Coulomb potential dominates, and the effective potential is repulsive. In an intermediate concentration, the membrane-mediated attractive potentials compete with the screened Coulomb potentials and form an effective attractive well. With further increase of charged lipids, the mediated attractive potentials decay, and the screened Coulomb potentials dominate over the system again. If we calculate the line tension in this case, also, it has the same tendency as in the infinite-diluted case. However, we see from Fig.7 that on increasing the binding macroions, the attractive potential saturates at a certain concentration with $\sigma_c\tau^2 = 0.08$, which deviates slightly from the value $\sigma_c\tau^2 = 0.07$ where the line tension is maximum (Fig. 6). Such a deviation indicates that although line tension is still dominant for finite concentration of macroions, the bridge effect will become relatively stronger, compared to the infinite-diluted case.

V. CONCLUSION

In this paper, we have studied the membrane-mediated potential between the binding macroions which is induced by the interplay of the macroions and lipids. The process can be generally interpreted as follows. When the binding macroions are infinite dilute, the macroion will induce an enrichment of charged lipids under it. This process will be balanced by the decrease of the mixing entropy and the increase of repulsion between charged lipids. When there is a soft-core repulsion between charged and neutral lipids, the nonuniform distribution of lipids will introduce a line tension. The macroions prefer to aggregate together to reduce the line tension energy. This will compete with the screened Coulomb potential and form an attractive well in the effective potential. The bridging effect will also contribute to the attractive potential, but the line tension is dominant. Interestingly, as we increase the number density of charged lipids, but fix the total number density of lipids, we observe a repulsion - attraction - repulsion transition due to the competition between the line tension and screened electrostatic interactions. For the finite concentration case, we have to take into account the coupling effects between binding macroions. We find that with the increase of binding macroions, the line tension induced by a single binding macroion is gradually suppressed and the maximum of attractive potential will shift toward the higher values of charged lipid concentration σ_c. The result can be attributed to the competition of recruiting charged lipids due to different binding macroions. The effective potential calculated in this case is not as faithful as the infinite dilution case. But in the case where the concentration of binding macroions is fixed, the result obtained is physically reasonable.

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1. Bongrand, P. 1999. Ligand-receptor interactions. *Rep. Prog. Phys.* 62:921-968.

2. Simons, K., and E. Ikonen. 1997. Functional rafts in cell membranes. *Nature.* 387:569-572.

3. Lipowsky, R., and R. Dimova. 2003. Domains in membranes and vesicles. *J. Phys.: Condens. Matter.* 15:S31-S45.

4. Ben-Tal, N., B. Honig, R. M. Peitzsch, G. Denisov, and S. Mclaughlin. 1996. Binding of small basic peptides to membranes containing acidic lipids: theoretical models and experimen-

tal results. *Biophys. J.* 71:561-575.
5. Denisov, G., S. Wanaski, P. Luan, M. Glaser, and S. Mclaughlin. 1998. Binding of basic peptides to membranes produces lateral domains enriched in the acidic lipids phosphatidylserine and phosphatidylinositol 4,5-bisphosphate: an electrostatic model and experimental results. *Biophys. J.* 74:731-744.
6. Heimburg, T., B. Angerstein, and D. Marsh. 1999. Binding of peripheral proteins to mixed lipid membranes: effect of lipid demixing upon binding. *Biophys. J.* 76:2575-2586.
7. Hinderliter, A., P. F. F. Almeida, C. E. Creutz, and R. L. Biltonen. 2001. Domain Formation in a fluid mixed lipid bilayer modulated through binding of the C2 protein motif. *Biochemistry.* 40:4181-4191.
8. Hinderliter, A., R. L. Biltonen, and P. F. F. Almeida. 2004. Lipid modulation of protein-induced membrane domains as a mechanism for controlling signal transduction. *Biochemistry.* 43:7102-7110.
9. May, S., D. Harries, and A. Ben-Shaul. 2000. Lipid demixing and protein-protein interactions in the adsorption of charged proteins on mixed membranes. *Biophys. J.* 79:1747-1760.
10. May, S., D. Harreis, and A. Ben-Shaul. 2002. Macroion-induced compositional instability of binary fluid membranes. *Phys. Rev. Lett.* 26:268102.
11. May, S. 2005. Stability of macroion-decorated lipid membranes. *J. Phys.: Condens. Matter.* 17:R833-R850.
12. Mbamala, E. C., A. Ben-Shaul, and S. May. 2005. Domain formation induced by the adsorption of charged proteins on mixed lipid membranes. *Biophys. J.* 88:1702-1714.
13. Haleva, E., N. Ben-Tal, and H. Diamant. 2004. Increased concentration of polyvalent phospholipids in the adsorption domain of a charged protein. *Biophys. J.* 86:2165-2178.
14. Neu, J. C. 1999. Wall-mediated forces between like-charged bodies in an electrolyte. *Phys. Rev. Lett.* 82:1072-1074.
15. Naji, A., S. Jungblut, A. G. Moreira, and R. R. Netz. 2005. Electrostatic interactions in strongly coupled soft matter. *Physica A.* 352:131-170.
16. Levin, Y. 2005. Strange electrostatics in physics, chemistry, and biology. *Physica A.* 352:43-52.
17. Levin, Y. 2002. Electrostatic correlations: from plasma to biology. *Rep. Prog. Phys.* 65:1577-1632.
18. Wu, J., D. Bratko, and J. M. Prausnitz. 1998. Interaction between like-charged colloidal spheres in electrolyte solutions. *Proc. Natl. Acad. Sci. USA.* 95:15169-15172.
19. Allahyarov, E., I. D'Amico, and H. Löwen. 1998. Attraction between like-charged macroions by coulomb depletion. *Phys. Rev. Lett.* 81:1334-1337.
20. Linse, P., and V. Lobaskin. 1999. Electrostatic attraction and phase separation in solutions of like-charged colloidal particles. *Phys. Rev. Lett.* 83:4208-4211.
21. Hribar, B., and V. Vlachy. 2000. Clustering of macroions in solutions of highly asymmetric electrolytes. *Biophys. J.* 78:694-698.
22. Kepler, G. M., and S. Fraden. 1994. Attractive potential between confined colloids at low ionic strength. *Phys. Rev. Lett.* 73:356-359.
23. Behrens, S. H., and D. G. Grier. 2001. Pair interaction of charged colloidal spheres near a charged wall. *Phys. Rev. E.* 64:050401.
24. Han, Y. L., and D. G. Grier. 2003. Confinement-induced colloidal attractions in Equilibrium. *Phys. Rev. Lett.* 91:038302.
25. Caccamo, C. 1996. Integral equation theory description of phase equilibria in classical fluids.

Phys. Rep. 274:1-105.
26. Hansen, J. P., and I. R. McDonald. 1986. Theory of Simple Liquids, 2nd Ed. Academic Press, London.
27. Tohver, V., J. E. Smay, A. Braem, P. V. Braun, and J. A. Lewis. 2001. Nanoparticle halos: A new colloid stabilization mechanism. *Proc. Natl. Acad. Sci. USA.* 98:8950-8954.
28. Karanikas, S., and A. A. Louis. 2004. Dynamic colloidal stabilization by nanoparticle halos. *Phys. Rev. Lett.* 93:248303.
29. Chen, K., and Y. Q. Ma. 2005. Interactions between colloidal particles induced by polymer brushes grafted onto the substrate. *J. Phys. Chem. B.* 109:17617-17622.
30. Feller, S. E., R. M. Venable, and R. W. Pastor. 1997. Computer simulation of a DPPC phospholipid bilayer: structural changes as a function of molecular surface area. *Langmuir.* 13:6555-6561.
31. Lagüe, P., M. J. Zuckermann, and B. Roux. 2000. Lipid-mediated interactions between intrinsic membrane proteins: a theoretical study based on integral equations. *Biophys. J.* 79:2867-2879.
32. Rosenfeld, Y., and N. W. Ashcroft. 1979. Theory of simple classical fluids: universality in the short-range structure. *Phys. Rev. A.* 20:1208-1235.
33. Coster, H. G. L. 2003. The physics of cell membranes *J. Biol. Phys.* 29:363-399.
34. Lado, F. 1971. Numerical fourier transforms in one, two, and three dimensions for liquid state calculations. *J. Comput. Phys.* 8:417-433.
35. Yethiraj, A., B. J. Sung, and F. Lado. 2005. Integral equation theory for two-dimensional polymer melts. *J. Chem. Phys.* 122:094910.
36. Asakura, S., and F. Oosawa. 1954. On interaction between two bodies immersed in a solution of macromolecules. *J. Chem. Phys.* 22:1255-1256.
37. Reatto, L., D. Levesque, and J. J. Weis. 1986. Iterative pedictor-corrector method for extraction of the pair interaction from structrual data for dense classical liquids. *Phys. Rev. A.* 33:3451-3465.

Figure captions:

Figure 1: Schematic of a macroion bound to a binary fluid lipid membrane. The lipid is treated as a hard-sphere head with a radius of r_{ch}(charged lipid) or r_{nh}(neutral lipid) and a soft-core repulsion tails. The binding macroions are treated as uniformly charged hard spheres with radius r_p. There is a separation h from the membrane to the bottom of the macroion. The system is a three-dimensional system, but can be effectively mapped into a two-dimensional one when h is fixed.

Figure 2: The effective pair potentials $\beta V_{pp}^{eff}(r)$ or $\beta V_{pp}^{m}(r)$ $(= \beta V_{pp}^{eff}(r) - \beta V_{pp}(r))$ change with $\beta\omega_{cn}$. The macroion's diameter is chosen to be 8τ, and the effective charges of the macroions and charged lipids is $Z_p = 6e$ and $Z_c = -1e$, respectively. The mediated potential $\beta V_{pp}^{m}(r) = \beta V_{pp}^{eff}(r) - \beta V_{pp}(r)$ becomes more attractive with the increase of $\beta\omega_{cn}$. This is a general behavior of the system.

Figure 3: The total correlation functions $h_{pn}(r)$ and $h_{pc}(r)$ between the lipids and macroion for varying values of $\beta\omega_{cn}$. In (b), the curves for the lateral distance $r > 12\tau$ is enlarged, and re-plotted in the inset, showing the correlation effects which will not appear in the mean field approximation.

Figure 4: The total correlation function $h_{pc}(r)$ verse $\beta\omega_{cn}$ for $Z_c = -2e$.

Figure 5: Effective pair potential $\beta V_{pp}^{eff}(r)$ verse the number density of charged lipids for fixed total lipids concentration $(\sigma_c + \sigma_n)\tau^2 = 0.16$ and $\beta\omega_{cn} = 2.0$. The attractive potential saturates at an intermediate concentration $(\sigma_c\tau^2 = 0.05)$ of charged lipids.

Figure 6: Single macroion induced line tension as a function of $\sigma_c\tau^2$ for fixed total lipids concentration $(\sigma_c + \sigma_n)\tau^2 = 0.16$ and $\beta\omega_{cn} = 2.0$. The solid square curve shows the case $\sigma_p\tau^2 \to 0$, and the line tension saturates at $\sigma_c\tau^2 = 0.05$. As the binding macroions are increased, The line tension decreases, and the position of maximum line tension moves toward the higher values of $\sigma_c\tau^2$.

Figure 7: Effective pair potential $\beta V_{pp}(r)$ for varying concentrations of charged lipids with $(\sigma_c + \sigma_n)\tau^2 = 0.16$, $\beta\omega_{cn} = 2.0$, and $\sigma_p\tau^2 = 0.004$. The attractive potential saturates at an intermediate concentration $\sigma_c\tau^2 = 0.08$.

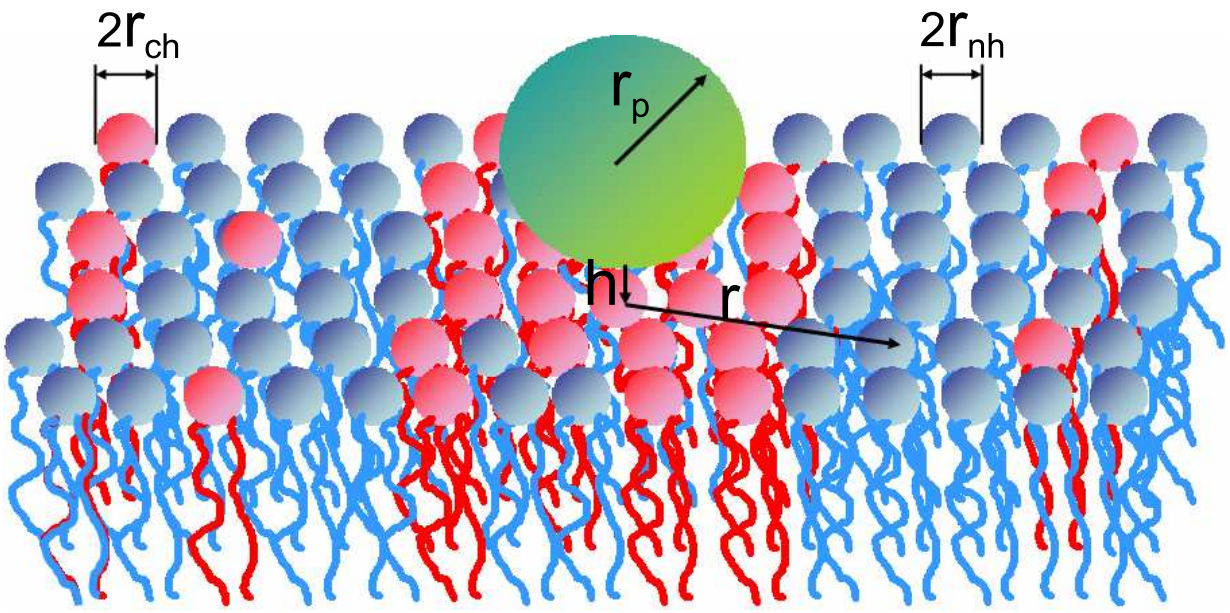

FIG. 1:

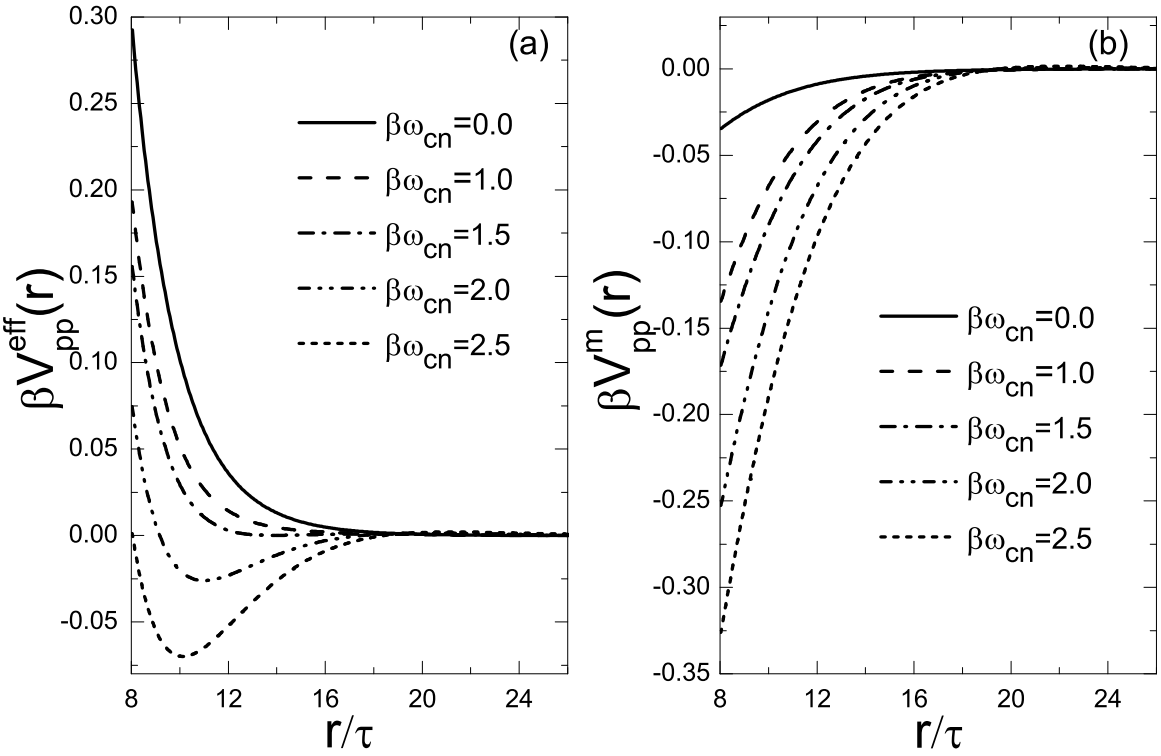
(a)
(b)
βω_cn=0.0
βω_cn=1.0
βω_cn=1.5
βω_cn=2.0
βω_cn=2.5
βV^eff_pp(r)
βV^m_pp(r)
r/τ
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
-0.10
-0.15
-0.20
-0.25
-0.30
-0.35
8
12
16
20
24

FIG. 2:

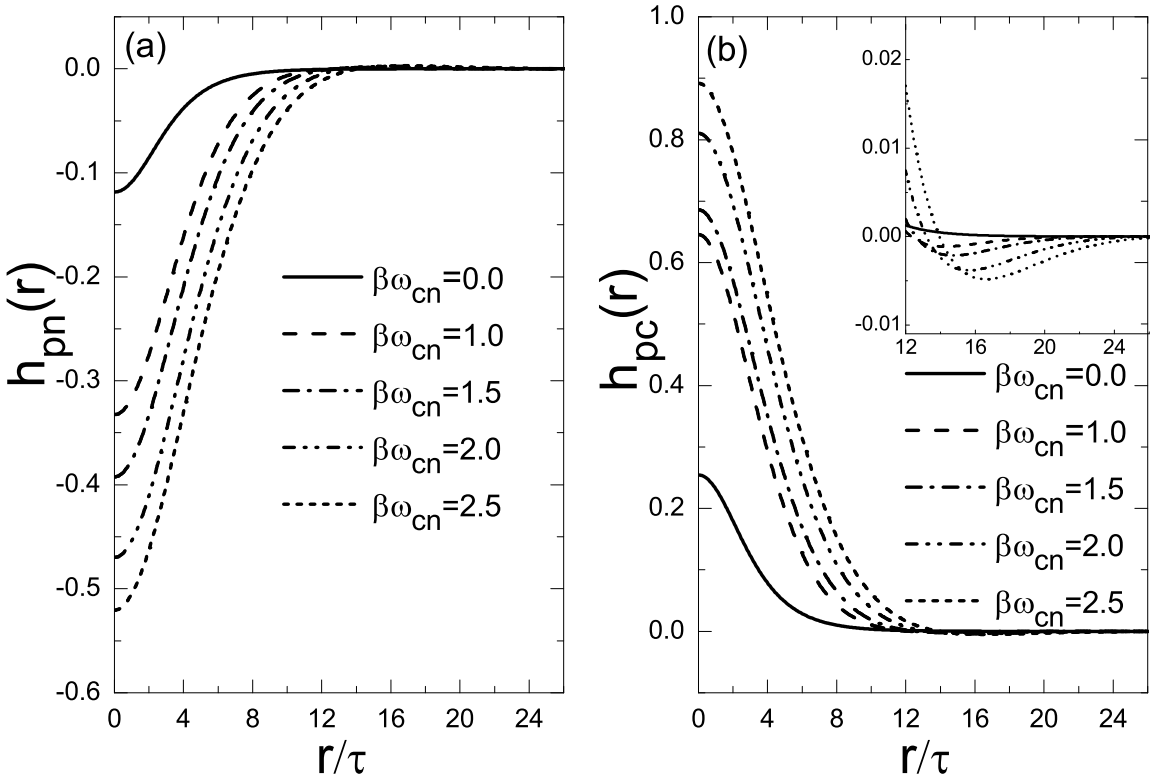
(a)
$h_{pn}(r)$
r/τ
$\beta\omega_{cn}$=0.0
$\beta\omega_{cn}$=1.0
$\beta\omega_{cn}$=1.5
$\beta\omega_{cn}$=2.0
$\beta\omega_{cn}$=2.5
(b)
$h_{pc}(r)$
r/τ
$\beta\omega_{cn}$=0.0
$\beta\omega_{cn}$=1.0
$\beta\omega_{cn}$=1.5
$\beta\omega_{cn}$=2.0
$\beta\omega_{cn}$=2.5

FIG. 3:

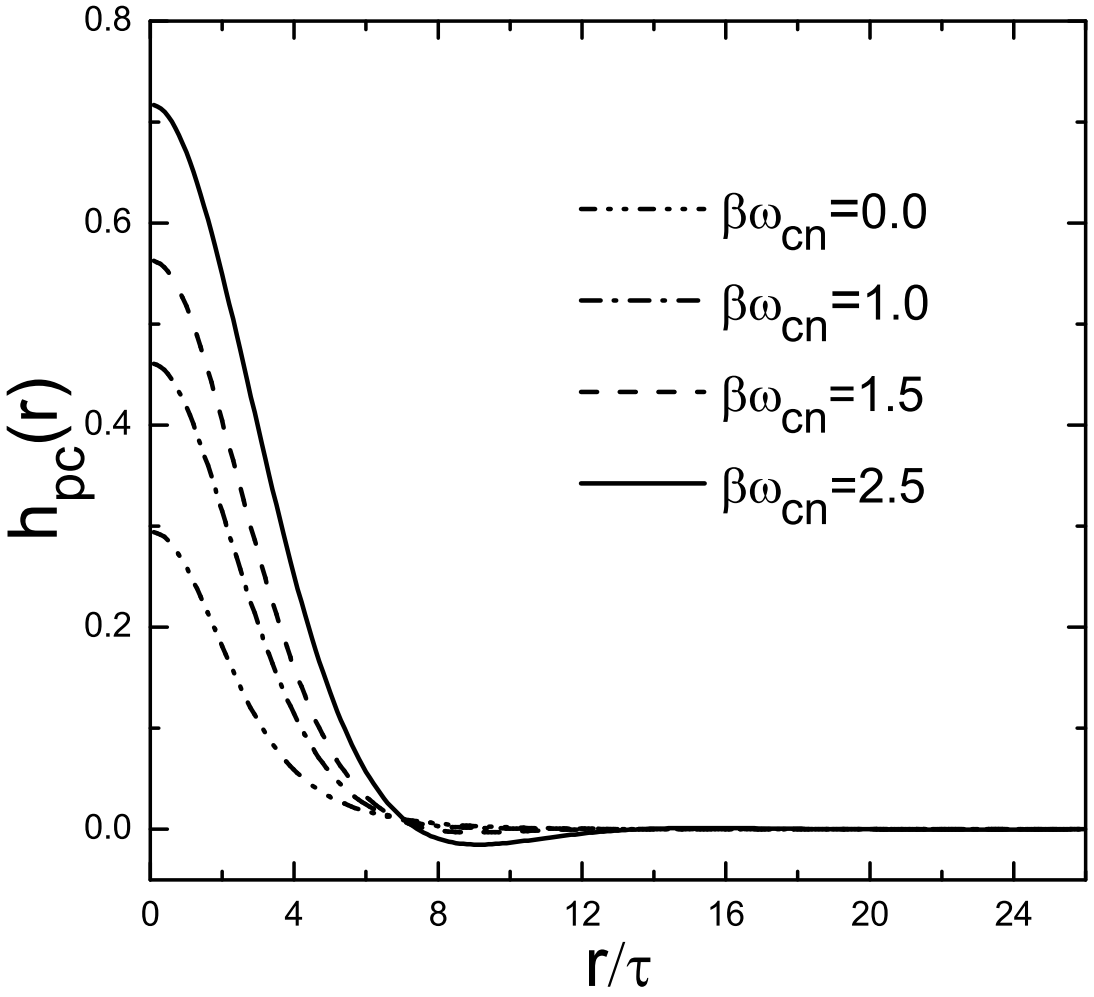
0.8
0.6
0.4
0.2
0.0
0
4
8
12
16
20
24
$h_{pc}(r)$
r/τ
$\beta\omega_{cn}$=0.0
$\beta\omega_{cn}$=1.0
$\beta\omega_{cn}$=1.5
$\beta\omega_{cn}$=2.5

FIG. 4:

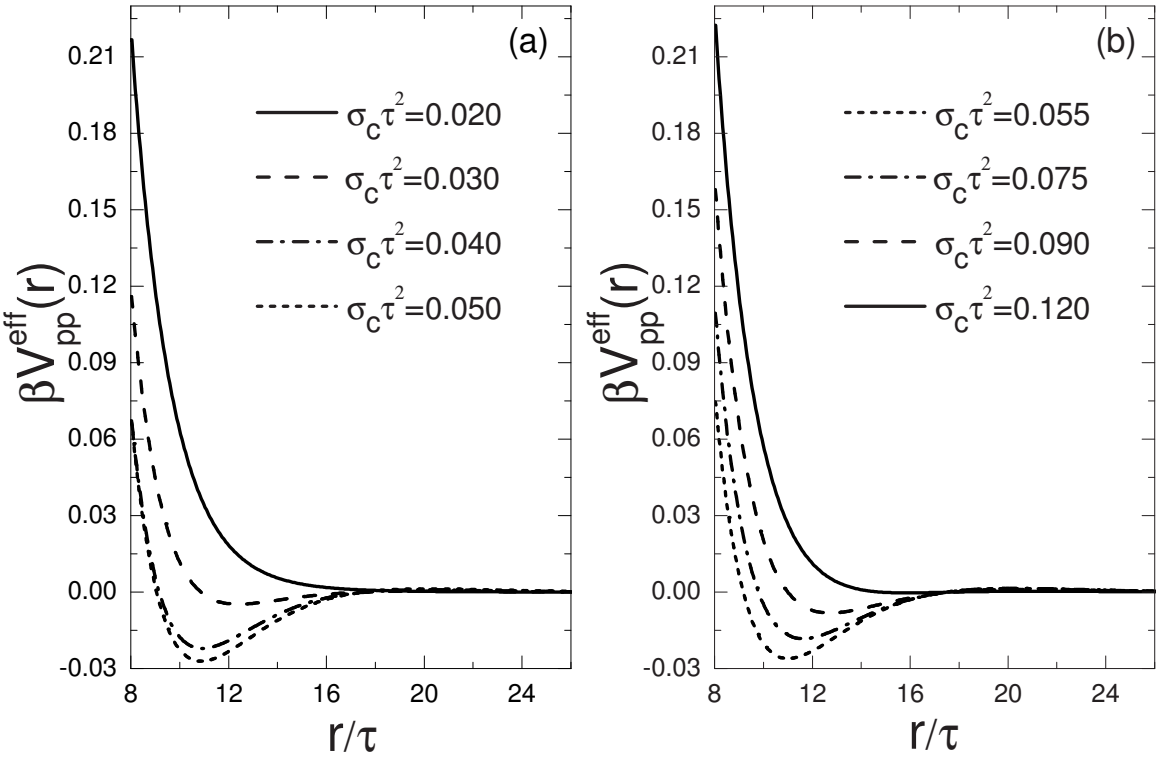
(a)
(b)
$\beta V_{pp}^{eff}(r)$
r/τ
$\sigma_c\tau^2$=0.020
$\sigma_c\tau^2$=0.030
$\sigma_c\tau^2$=0.040
$\sigma_c\tau^2$=0.050
$\sigma_c\tau^2$=0.055
$\sigma_c\tau^2$=0.075
$\sigma_c\tau^2$=0.090
$\sigma_c\tau^2$=0.120
0.21
0.18
0.15
0.12
0.09
0.06
0.03
0.00
-0.03
8
12
16
20
24

FIG. 5:

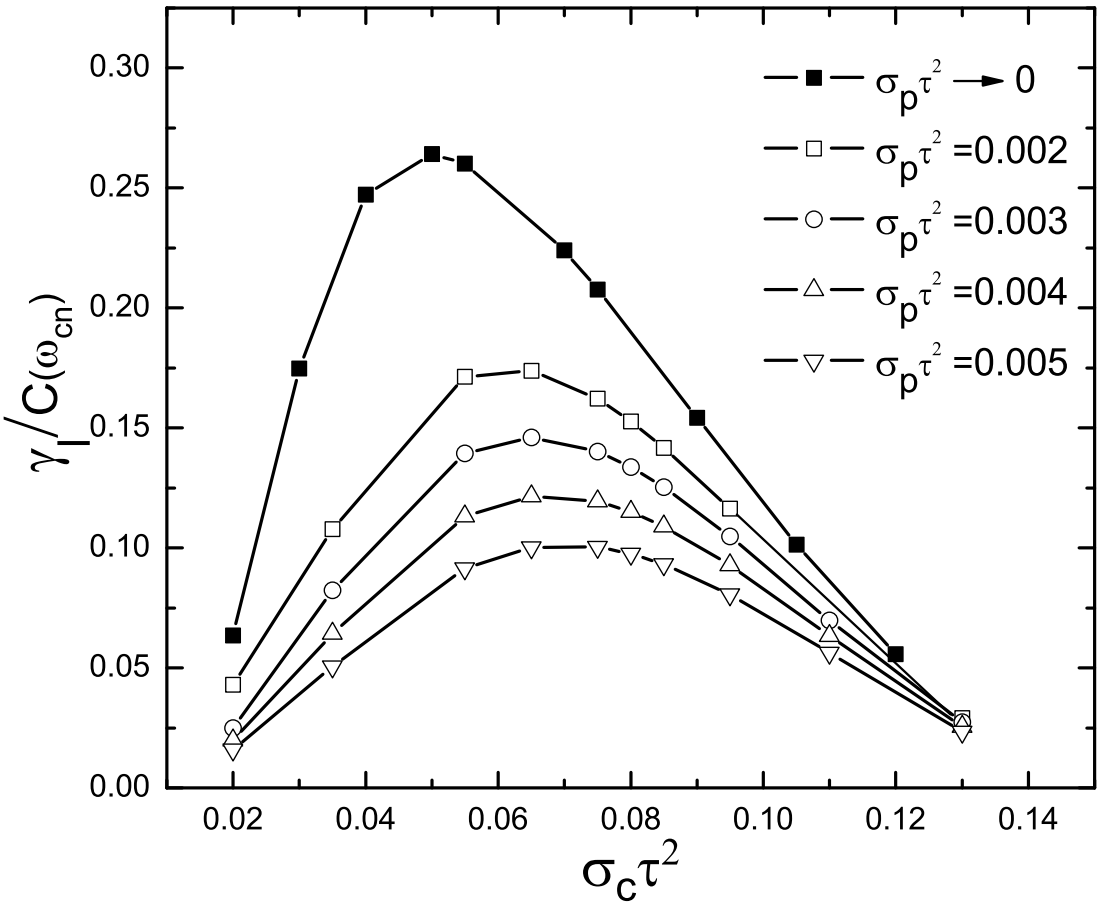
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0.14
$\gamma_I/C(\omega_{cn})$
$\sigma_c\tau^2$
$\sigma_p\tau^2 \rightarrow 0$
$\sigma_p\tau^2$ =0.002
$\sigma_p\tau^2$ =0.003
$\sigma_p\tau^2$ =0.004
$\sigma_p\tau^2$ =0.005

FIG. 6:

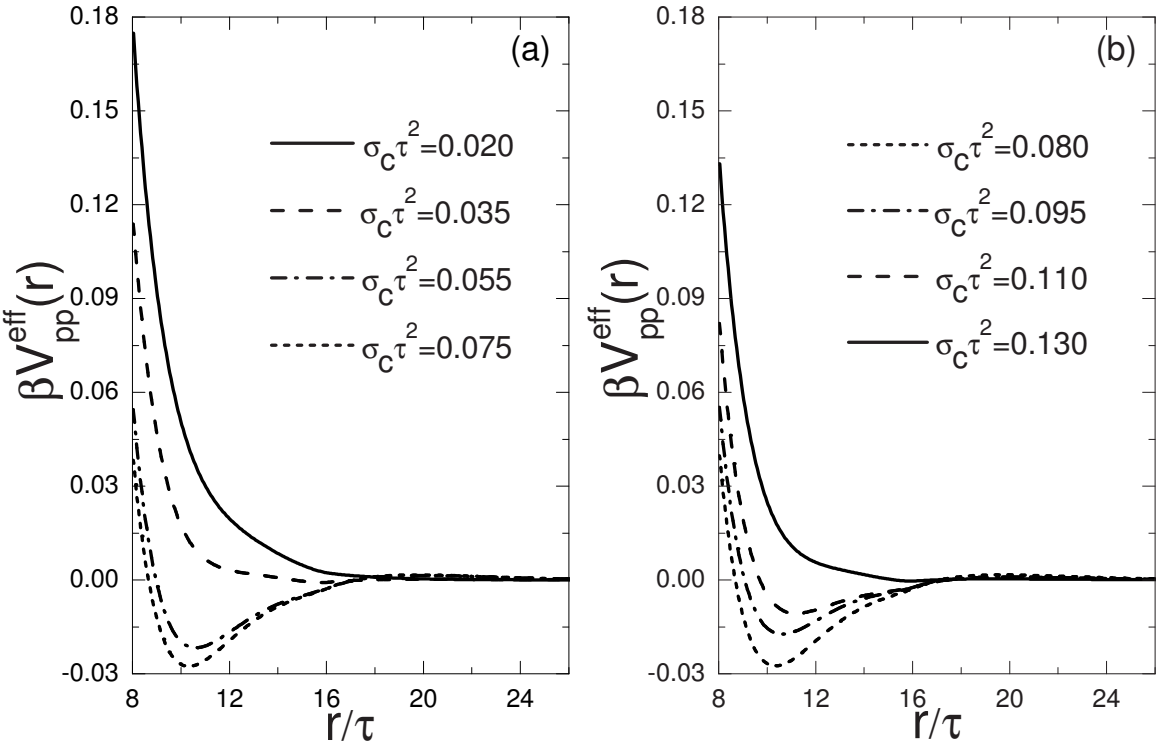
(a)
(b)
$\beta V_{pp}^{eff}(r)$
r/τ
$\sigma_c\tau^2$=0.020
$\sigma_c\tau^2$=0.035
$\sigma_c\tau^2$=0.055
$\sigma_c\tau^2$=0.075
$\sigma_c\tau^2$=0.080
$\sigma_c\tau^2$=0.095
$\sigma_c\tau^2$=0.110
$\sigma_c\tau^2$=0.130
0.18
0.15
0.12
0.09
0.06
0.03
0.00
-0.03
8
12
16
20
24

FIG. 7: